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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,288	LARSEN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-13,17,24-26,28-37 and 44-56* is/are pending in the application.

4a) Of the above claim(s) *24-26 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-13,17,28-37,44-52 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 11/12/04, has been entered.
Claims 7-8, 14-16, 18-23, 27 and 38-43 have been canceled.
Claims 1, 6, 9, 13, 24, 28-34 and 37 have been amended.
Claims 44-56 have been added.

Claims 1-6, 9-13, 17, 24-26, 28-37 and 44-56 are pending.

2. Applicant's election of the following species:
the alkylating agent is busulfan;
the first ligand is a soluble CTLA4;
the second ligand is anti-CD40 antibody; and
the targeted condition is solid organ or tissue/cellular transplant
with traverse is acknowledged.

The traversal is on the ground(s) that it would not be undue burden. This is not found persuasive because of the reasons of record set forth in the species election. MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required. Regarding applicant's comments about undue burden, the MPEP 803 states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Species Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that examination Groups require non-coextensive searches. The Inventions are distinct for reasons elaborated in the previous Office Action.
The requirement is still deemed proper and is therefore mad

As pointed out previously, should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

Applicant has not indicated that the species are obvious variants.

Claims 24-26 and 53 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected inventions / species.

Claims 1-6, 9-13, 17, 28-37 and 44-52 and 54-56 are being examined to the extent that they read on the elected species (e.g. busulfan, the first ligand is a soluble CTLA4, the second ligand is anti-CD40 antibody and the targeted condition is solid organ or tissue/cellular transplant) for examination purposes in the instant application.

Applicant is reminded to employ the proper amendment practice, according to the requirements of 37 CFR 1.121, as amended on June 30, 2003 (see 68 Fed. Reg. 38611, June 30, 2003).

Applicant has not provided the proper status identifier for each claim.

For example, claim 24 has been "withdrawn" from consideration as being drawn to a non-elected invention;
claims 28-29 are under consideration as being drawn to the elected species; and
claim 51 is under consideration as being drawn to the elected species (e.g. the broadest reasonable interpretation of the "ligand for CD40" reads on "an antibody that bind CD40", which is one of the elected species".

3. Upon a review of the instant application, it is not clear that the instant application is compliance with the sequence rules.

For example, page 79 of the instant discloses "MYPPY" in the absence of a SEQ ID NO.

Applicant is required to review the instant application for compliance with the requirements of applications which contain sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825. If the instant application does not have an appropriate SEQ ID NO: for each disclosed sequence, then applicant must comply with the Sequence Rules as set forth in 37 CFR 1.821-1.825.

4. The filing date of the instant claims is deemed to be the filing date of priority application USSN 60/303,142, filed 7/5/01.

Priority application USSN 60/264,528, filed 1/26/01 does not appear to support the instant claims encompassing methods of inhibiting rejection of a solid organ or tissue/cellular transplant with by administering an alkylating agent (e.g. bulsufan) and subsequently administering T cell depleted bone marrow cells before, during or after as the transplant, as well as administering CD28 / CD80 / CD86 / CD154 / CD40 inhibitors.

If applicant desires priority prior to 7/5/01; applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earliest priority application asserted. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

6. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

It is noted that "BALB/c" is the proper designation of this mouse strain (e.g. see instant Examples).

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 45-50 and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "the specific mutant CTLA4 molecules such as the L104EA29YIg molecule disclosed in the specification as filed or claimed (e.g. see Example 8 on pages 67-83 of the instant specification), does not reasonably provide enablement for any "CTLA4 mutant molecule" to be employed as an immunosuppressive agent in the instant claimed methods.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any "CTLA4 mutant molecule" that inhibits graft rejection encompassed by the claimed methods. "CTLA4 mutant molecule" may have some notion of the source of the "first ligand that interferes with binding of CD28 to either CD80 or CD86", however, claiming biochemical molecules by a particular name and a modification of said molecule (e.g. "CTLA4 mutant molecule") by applicant fails to distinctly claim what that "CTLA4 mutant molecule" is and what it is made up of or how it differs from native CTLA4. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "CTLA4 mutant molecule".

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of "CTLA4 mutant molecules". The instant invention encompasses any "CTLA4 mutant molecule", yet the instant specification does not provide sufficient guidance and direction as to the selection of particular sequences essential for the unrecited (claim 47) and recited function (see claim 48), which interferes with binding of CD28 to either CD80 or CD86in the inhibition of graft rejection.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "B7 antigens or antigenic fragments" other than the B7 or B7Ig disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of ligand and receptors encompassed by the claimed invention.

Attwood (Science 290: 471–473, 2000) notes in the Introductory paragraphs that it is presumptuous to make functional assignments merely on the basis of some degrees of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tellus functions").

Skolnick et al. (Trends in Biotechnology 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

This requirement is emphasized in the instant example since, as summarized in Figures 2 and 3 of Coyle et al. (Nature Immunology 2: 203-209, 2001) the B7-like family members have distinct expression patterns and distinct functions.

Metzler et al. (Nature Structural Biology 4: 527- 531, 1997) describe various CTLA4 mutants and their varying effects on CD80 and CD86 binding (see entire document, including Table 2 on page 530). Here, there does not appear sufficient predictability as to those mutations that result in a particular function, as the mutations had multiple effects on said CD80 and CD86 binding, including little or no effects.

Thus, the experimentation left to those skilled in the art to determine the function of the scope of "CTLA4 mutant molecules" that interfere with binding of CD28 to either CD80 and CD86 and inhibit graft rejection encompassed by the claimed invention is unnecessarily and improperly extensive and undue.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of "CTLA4 mutant molecules". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "CTLA4 mutant molecules" other than those specific "CTLA mutant molecules" which interfere with the binding of CD28 to either CD80 or CD86 as disclosed in the specification as filed (or as recited in claims 49-50) as the first ligand in the claimed methods to inhibit graft rejection.

Applicant is invited to limit the claims to those "CTLA4 mutant molecules" with the appropriate inhibitory properties disclosed in the specification as filed as the first ligand in the claimed methods.

10. Claims 50 and 56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that L104EA29YIg CTLA4 mutant molecule is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell line / plasmid which produces this CTLA4 mutant molecule. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

It does not appear from the record, including page 70, paragraph 2 of the instant specification that that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications has been set forth in the instant application.

Alternatively, it is noted that the sequence of an entire biological material such as the L104EA29YIg CTLA4 mutant molecule satisfies the biological deposit of said L104EA29YIg CTLA4 mutant molecule. Note that satisfaction for the biological deposit of the L104EA29YIg CTLA4 mutant molecule requires the disclosure and recitation of its entire amino acid sequence and not based upon partial sequences.

11. Claims 50 and 56 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50 and 56 are indefinite in the recitation of "L104EA29Ylg" because its characteristics are not known. The use of "L104EA29Ylg as the sole means of identifying the claimed CTLA mutant molecule renders the claim indefinite because ""L104EA29Ylg" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct biological materials.

In addition, claim 50 is objected to as it appears that the claimed recitation employs the number 1 (one) rather than a capital letter I in the recitation of "L104EA29Ylg". The proper designation is "Ig" not "1g" at the end of the lab designation to signify immunoglobulin.

It appears that the recitation of "L104EA29Ylg" in claim 56 is proper.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-6, 9-13, 17, 28-29, 34-37, 48 and 51-55 are rejected under 35 U.S.C. § 102(e) as being anticipated by Sykes (U.S. Patent No. 6,514,513) (see entire document).

Sykes teach methods inducing specific nonresponsiveness or tolerance to various antigens by inducing hemopoietic chimerism, including transplant antigens by administering
T cell depleted bone marrow cells / stem cells (e.g. see columns 6-7; column 8, lines 53-55; columns 9-11, column 15, paragraph 1) (note stem cells read on T cell depleted bone marrow cells);
hemopoietic space agents, including busulfan (e.g. see column 8, paragraph 1);,
CD40L-CD40 inhibitors, including antibodies that bind CD40 and
CD28-B7 inhibitors, including CTLA4Ig (e.g. see column 8, line 65- column, line 36; column 12)
as it relates to tissue and organ transplantation (see entire document, including Summary of the Invention; Detailed Description; Claims).

In addition, Sykes describes numerous modes of administration of providing the above-mentioned elements of therapeutic regimen in combination before, concurrently and subsequent to transplantation (see Summary of the Invention and Detailed Description).

Administering bone marrow stem cells, including repeated administration of said cells prior to, during and after the transplant are described (see Summary of the Invention, including column 2, line 60 – column 3, line 49; and Detailed Description, including column 6, line 38 – column 7, line 46; columns 9 – 10)

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to promote long term graft acceptance of cells, tissues and organs with stem cells, CD40L-CD40 inhibitors, including antibodies that bind CD40, and CD28-B7 inhibitors, including CTLA4Ig as well as the akylating agent bulsulfan.
It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

15. Claims 1-2, 9-10 and 30-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513) in view of art known practice and modes of administration of alkylating agents such as bulsulfan at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994)

Sykes teach methods inducing specific nonresponsiveness or tolerance to various antigens by inducing hemopoietic chimerism, including transplant antigens by administering
T cell depleted bone marrow cells / stem cells (e.g. see columns 6-7; column 8, lines 53-55; columns 9-11, column 15, paragraph 1) (note stem cells read on T cell depleted bone marrow cells);
hemopoietic space agents, including busulfan (e.g. see column 8, paragraph 1);,
CD40L-CD40 inhibitors, including antibodies that bind CD40 and
CD28-B7 inhibitors, including CTLA4Ig (e.g. see column 8, line 65- column, line 36; column 12)
as it relates to tissue and organ transplantation (see entire document, including Summary of the Invention; Detailed Description; Claims).

In addition, Sykes describes numerous modes of administration of providing the above-mentioned elements of therapeutic regimen in combination before, concurrently and subsequent to transplantation (see Summary of the Invention and Detailed Description).

Administering bone marrow stem cells, including repeated administration of said cells prior to, during and after the transplant are described (see Summary of the Invention, including column 2, line 60 – column 3, line 49; and Detailed Description, including column 6, line 38 – column 7, line 46; columns 9 – 10)

Sykes differs from the claimed methods by not disclosing the particular timing of busulfan in the claimed therapeutic methods to promote graft survival (e.g. see claims 30-32). Claims 1-2 and 9-10 encompass the particular timing of busulfan administration encompassed by claims 30-32.

As acknowledged on pages 26-27 of the instant specification including the citation of Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148; see entire documents); modes of administering busulfan were known at the time the invention was made. Therefore, one of ordinary skill in the art would have been motivated to administer busulfan at various times, including the claimed timing (e.g. see claims 30-32) to create hemopoietic space for T cell depleted bone marrow / stem cells as well as to optimize bioavailability.

Slattery et al. teach that busulfan is an alkylating agents commonly used to ablate marrow before hemopoietic stem cell transplantation and the importance of analytical and pharmacokinetic aspects of therapeutic monitoring (see entire document, including the Summary on page 543). It is noted that the patients revied bulsulfant doses every 6 hours over a period of 4 days (see Busulfan Concentration and Outcome of Transplantation).

Similarly Hassan et al. teach the known use of busulfan in myeloablative therapy in bone marrow transplantation and the importance of drug monitoring and individual dose adjustment in providing for busulfan bioavailability while reducing / avoiding drug-related toxicities (See entire document, including the Abstract).

Therefore, the claimed timing of busulfan in the claimed therapeutic methods to inhibit rejection of transplant was obvious to one of ordinary skill in the art at the time the invention was made, as these limitations appear to be consistent with those employed in the prior art and with providing busulfan efficacy and bioavailability, while minimizing drug associated toxicities.

Given the general applicability and desirability of the modes of inducing immunological nonresponsiveness to a variety of antigens, including a wide variety of cells, tissues and organs of interest, one of ordinary skill in the art would have been motivated to include the well known transplantation of skin grafts to the transplantation regimens taught by Sykes.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 1, 9 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 225).

The teachings of Sykes are set forth above.

Sykes differs from the claimed methods by not disclosing "skin" per se as the tissue of organ of interest for transplantation. Claims 1 and 9 encompass skin grafts as the tissue / organ transplant of the claimed methods

Larsen et al. teach modes of inhibiting immune responses, including rejection of various tissues and organs including skin (e.g. see column 2; column 6, paragraph 4) by blocking CD40:CD40L and CTLA4:CD28:B7 pathways in order to induce immunological unresponsiveness in the transplant recipient (see entire document, including Background of the Invention, Summary of the Invention, Detailed Description and Claims).

Given the general applicability and desirability of the modes of inducing immunological nonresponsiveness to a variety of antigens, including a wide variety of cells, tissues and organs of interest, as taught by Sykes and Larsen et al.,one of ordinary skill in the art would have been motivated to include the well known transplantation of skin grafts to the transplantation regimens taught by Sykes, given the evidence by Larsen et al. that skin is among a list of known tissues that were routinely transplanted at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 1, 5, 9, 11, 12 , 34-36, 44-52, 54, and 56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513) in view of Peach et al. (US 20020182211).

The teachings of Sykes are set forth above.

Sykes differs from the claimed methods by not disclosing the particular mutant CTLA4 mutant molecules, including L104EA29Yig CTLA4 recited in the instant claims as the inhibitory CTLA4 of the claimed invention.

Peach et al. teach soluble CTLA4 mutant molecules, including the specific L104EA29YIg, which have greater avidity than CTLA4 and can bind either of CD80, CD86 or both (e.g., see Summary of the Invention) in immunomodulating regimens for the treatment or prevention of acute or chronic graft rejection, including in combination therapy (e.g. see paragraphs [0079] – [0084] on pages 8-9). The claimed extracellular domains as well as the claimed sequences (e.g. claims 44-52 and 56) are intrinsic properties of the referenced CTLA4 mutant molecules, including the specific L104EA29YIg taught by Peach et al.

Given the greater avidity soluble CTLA4 mutant molecules, including the specific L104EA29YIg, which can bind either of CD80, CD86 or both, one of ordinary skill in the art would have been motivated to substitute said soluble CTLA4 mutant molecules taught by Peach et al. in the referenced transplantation regimens taught by Sykes, in an effort to increase the efficacy of CTLA4 molecules to inhibit the desired CTLA4-mediated responses in promoting long term graft survival at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
February 15, 2005